IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next of Kin of Richard Smith, Deceased,	)	
Plaintiff,	)	**CASE NO. 3:05-0444**
v.	)	**Judge Aleta A. Trauger**
PFIZER INC., et al,	)	
Defendants.	)	

EXPERT WITNESS STATEMENT OF CHARLES P. TAYLOR, JR., PH.D.

I. EXPERT QUALIFICATIONS

A. Personal Background

My name is Charles Taylor. I am 55, and I am a neuroscientist. In this case, I was asked to testify about the pharmacology of Neurontin, which means the way that Neurontin interacts with the body, and in particular the nervous system. As I will explain shortly, that is a subject that I spent a significant part of my professional career studying and writing about, and that will be my focus here today.

Let me begin with explaining a little about my background. I received a B.S. degree in zoology from the University of Texas in 1975, followed by a Ph.D. in neurobiology in 1980 from the University of California, Berkeley. From 1980 until 1982, I worked in a postdoctoral program sponsored by the federal government's National Institutes of Health ("NIH") at the Tulane University Medical Center. After that, I joined the research department at Parke-Davis in Ann Arbor, Michigan, and later worked with Pfizer after Pfizer merged with Warner-Lambert

and Parke-Davis in 2000. I worked there from 1982 until 2007. I still live outside Ann Arbor. I am now mostly retired, though I do work as a consultant.

Until recently, I was a member of several professional scientific organizations. These included the Society for Neuroscience and the American Epilepsy Society. I have presented scientific speeches on Neurontin and closely related compounds at the Society for Neuroscience, the American College of Neuropsychopharmacology, the American Academy of Neurology, the American Pain Society, the Society for Biological Psychiatry, and others, including numerous medical schools and universities.

A copy of my professional curriculum vitae, or "CV," that lists more details about my education and experience is marked as Exhibit 7417.

B. Background – Neurontin Research

In my positions at Parke-Davis and Pfizer, I personally conducted scientific research on Neurontin, and also supervised teams of researchers in Ann Arbor, Michigan, and Cambridge, England, who were studying Neurontin. The type of research I am talking about is what we call "preclinical" research, which is conducted in a scientific laboratory setting, as opposed to clinical trials, which are conducted in a clinical, doctor-patient setting. Scientific research into how a drug acts in the body is almost always done in a laboratory, and that is primarily the kind of work that I and my team did, and what I will be discussing today.

Depending on the year and the projects we were working on at any given time, I supervised between two and ten or more Neurontin researchers. My research teams were made up of scientists with a number of different specialties. For instance, over the years, I supervised about eight electrophysiologists, who studied electrical signaling in the nervous system; six biochemists who studied the effects of chemicals on communication between nerve cells; two pharmacologists who studied the protein molecules within the body that medicines stick to and

interact with; and four to five chemists who synthesized chemicals related to Neurontin in order for other scientists to study how they worked.

My Neurontin research, as well as that of the teams I supervised, focused on a number of areas. For instance, I researched what kind of molecules Neurontin binds or sticks to in the brain, and which kinds of molecules it does not bind to. I also examined how it is absorbed and moves through the body, a study area known as pharmacokinetics. I examined how Neurontin does or does not affect the activity of neurons and networks of neurons in the brain, and how it affects or doesn't affect the natural chemicals, known as neurotransmitters, that send signals from one neuron to another. Finally, I looked at how Neurontin acts on neurons to alter pain perception, seizures, or other medically relevant conditions in the body, and how it acts in the body to produce its beneficial and adverse effects.

As I mentioned, the vast majority of my research, and research like it done by others, was done in laboratories. Often such research is done with experimental animals, or with nerve cells "*in vitro*" (meaning, "in the glass"). Some of this research is done in hospitals on live patients, but actually very little. The reason animal and in vitro studies are used, and usually must be used, for this kind of research is simple: the brain and spinal cord in living people are not easily accessible. Only in some very limited circumstances can scientists conduct any kind of testing or measurements directly on the human brain. One rare circumstance that allows us to study human brain tissue is when patients who are having brain surgery that involves removing tissue to treat a disease volunteer to provide a sample of the tissue for research. Sometimes we also can do research that uses high-tech nuclear magnetic resonance imaging equipment (MRIs and other related techniques) to make images of living human brains, but that kind of study is often not very useful. This is because, unfortunately, taking an image of the brain can be compared to an

auto mechanic looking at an x-ray of an engine to see why it is not running smoothly, or why it won't start. You can't do it. So imaging can be a great tool to diagnose something like a tumor, but it does not often tell us how a medication is working. We have to study those questions in a laboratory, where we alter conditions and use lots of other probes that we really need to answer the questions.

Laboratory research to determine where a drug binds and how it works is very common. It is called preclinical research, and is done on every drug that is approved by the FDA or that is developed in this country, as well as in most other countries around the world. Almost all research on drug mechanisms of action is done in labs rather than in hospitals. Even though much of the lab testing is done on animals or is done using animal tissue, the results are very predictive and are reliably applicable to live humans.

Over the course of my 25-year scientific career with Pfizer, about 20-30% of my time has been spent studying Neurontin and closely related drugs. At times, I spent all my time on Neurontin research. In addition to my own research, I also kept abreast of research being done on Neurontin by many researchers outside of Pfizer. I regularly reviewed research on the drug published by individuals outside of the company. That was part of my job. Many times, I visited or spoke with other scientists who studied Neurontin.

I have published more than 35 peer-reviewed scientific journal articles, plus book chapters, and conference proceedings specifically referring to Neurontin and closely related compounds. Most recently, I published a peer-reviewed article that summarizes all the published literature about how Neurontin works in the body. It appeared in the journal *Pain* in 2009. Incidentally, I received no compensation or support from Pfizer for this article; I did it on my own time, because of my scientific interest alone.

As part of my work with this case, I was asked to examine the accuracy of Plaintiff's claims about Neurontin's mechanism of action in the brain, and how it supposedly leads to suicide. I am familiar with the state of scientific knowledge today about how Neurontin works in the human brain and central nervous system. I am familiar with the expert reports of the plaintiff's expert witness Dr. Trimble. I have read his report as well as the articles and materials he cited in that report. I also attended the deposition of Dr. Trimble. I am very familiar with his claims and opinions about how Neurontin supposedly works in the body, and the rationale and material he cites in support of his theories. I, in turn, have formed opinions about whether his theories are scientifically valid, and I am prepared to tell you what my opinions are and the basis for those opinions, which I will turn to now.

II. NEURONTIN AND ITS EFFECTS

A. The Functioning of the Brain

To understand what science tells us about where and how Neurontin acts in the nervous system and what it does and doesn't do, we have to understand some basic information about nerves.

First, as you may know, the brain and spinal cord are made up of many different nerve cells, called neurons. There are many, many millions of neurons that make up every person's brain and central nervous system. The brain and nerves work by sending signals from neuron to neuron, from one part of the body to another. Each neuron has hundreds of special connections with other neurons, creating a huge network.

Demonstrative 1 (Brain-Neuron-Synapse)

If we look at a tiny part of the brain through a microscope, we can see the individual nerve cells, called neurons, that make up the human brain. The connection between two neurons is called a synapse. This chart shows first the brain as a whole, then a diagram of a pair of

neurons, and finally, a diagram of a synapse, which is the tiny and very specialized space between two adjacent nerves. The colored pictures are images of neurons from an actual brain, and they correspond to the diagrams on the chart, which I took from a book published by the U.S. Surgeon General. Here you see one neuron, another neuron, and the part where they connect is the synapse, with its specialized structure for sending messages.

For the nervous system to work, signals have to pass across those synapses continuously and reliably. Signals are carried across the synapses by tiny packets of special chemicals called neurotransmitters. "Neuro" refers to nerves, and "transmitter" means carrying signals, so that's why they are called neurotransmitters. There are dozens of different neurotransmitters within the brain. About ten of these types are very common and important for how medicines work. We will talk about some of these neurotransmitters shortly.

Demonstrative 1 (Brain-Neuron-Synapse)

When they are not carrying signals from one nerve to the next, the neurotransmitter is stored in small packets at the end of each neuron. These storage packets are called vesicles. The small dots in the picture labeled "Synapse" on this chart represent molecules of neurotransmitter. As you can see, most of the vesicles are sitting and waiting to be used. The bright gold-colored areas on the picture of the nerve endings show us vesicles with neurotransmitter inside, and you can see them drawn on the diagram as well. On the diagram, the small dots between the two nerve endings represent neurotransmitter that has been released into the synapse, where they can rapidly carry signals across the space to the next neuron.

Demonstrative 2 (Synapse: Basic Parts and Functions)

On the surface of each neuron, there are locations, made of very special proteins, where a specific kind of neurotransmitter can stick or "bind' and send the signal onward. The special

proteins are called receptors because they are the spots where the neurotransmitter signal is received. You might think of this like a lock and key, or an electrical plug and a socket—the neurotransmitter fits a specific kind of receptor and not others. These are shown on the picture labeled "synapse."

Demonstrative 2 (Synapse: Basic Parts and Functions)

Another important part of nerves in terms of understanding how Neurontin works is also shown on this chart. The surfaces of the neurons have tiny holes or pores called calcium channels. Calcium channels can be thought of as a hole that opens and closes, but that only allows calcium into the neuron. Calcium is important because it is one of the things that controls the release of transmitters.

To relate these parts of nerves to how drugs work, the important thing to understand is that many of these different structures are the binding sites for medications that we commonly use. For instance, most antianxiety medicines, antidepressant medicines, and antiepileptic medicines bind and influence one of the various different sites within nerve synapses that we have been looking at.

B. Neurontin's Mechanism of Action

Now that we have looked at the nerves themselves and have a sense of how they work, I can explain what we have learned over the years about Neurontin's mechanism of action, including what it does, and what it does not do.

When Neurontin was developed back in the 1970s, it was a completely new molecule. It was not just a new variation of a drug that already existed and that had been previously studied. Chemically, Neurontin is similar to, but not the same as, a couple of the body's natural substances. One thing it is similar to in some respects is a neurotransmitter called GABA. Another similar chemical to Neurontin is one of the amino acids that we get in our food, called

L-isoleucine. Although all three are similar substances, they are not exactly the same, and even slight differences can make big changes in how a chemical substance will act in the body.

For that reason, we and other researchers had to develop and test many possible theories about how Neurontin works in the body. We had to learn where it binds to the nerve cells, and whether it affected any part of the nerve signaling process that we talked about earlier. Each of these possibilities, or hypotheses, had to be tested and re-tested to make sure the results were reliable. This kind of testing, over more than 20 years, has told us quite a lot about what Neurontin does and does not do.

Demonstrative 3 (FDA Labeling – Calcium Channel Subunit (Alpha-2-Delta) is the Molecular Target for Neurontin)

This chart shows language from the FDA-approved labeling for Neurontin about how it works. This section of the labeling, which is FDA's summary of Neurontin's pharmacology, is based on the preclinical testing that was completed before Neurontin was first approved back in 1993. It is very technical, but let me just point out the part that is relevant to my opinions and try to make it understandable. Where the FDA language says "a subunit of voltage-activated calcium channels," this refers specifically to the calcium channels that we looked at earlier. It is my opinion that Neurontin functions by binding to that alpha-2-delta site.

I now need to show you more about that site, and what that means in terms of Neurontin's action in the body, including whether or not Neurontin has any clinically significant impact on GABA or serotonin function after it sticks or binds at that spot within the brain.

Demonstrative 4 (Calcium Channels: Alpha-2-Delta Site)

This chart shows you a diagram and actual images of a calcium channel and the part of it called the alpha-2-delta site. The images you see here were made with a very powerful kind of microscope, called an electron microscope. Computers were used to generate the three-

dimensional structure from hundreds of separate images like the one shown by scientists in Massachusetts in 2003. The alpha-2-delta subunit was first discovered by scientists in Seattle in 1987, and its gene and protein sequence was first studied by scientists in San Diego in 1988.

The fact that Neurontin binds at this particular spot, the alpha-2-delta site on the calcium channel, was discovered in 1995, by Nicholas Gee and Jason Brown, in Cambridge, England. All of these findings were published in peer-reviewed scientific journals.

Because of where it sticks or binds to the calcium channel, Neurontin and a small number of other drugs that act similarly are called alpha-2-delta drugs. Many medicines are named for where they stick, or bind, within the body. For example, beta blockers, selective serotonin reuptake inhibitors (or "SSRIs"), angiotensin-converting enzyme Inhibitors (or "ACE inhibitors"), and antihistamines, are all medicines named for their active binding sites. Alpha-2-delta medicines like Neurontin are named for the protein molecule on nerve cells that they bind to, and that specific site is what you see in the images and diagram on this chart.

How does this binding at the alpha-2-delta site relate to Neurontin's mechanism of action? Remember that earlier I explained that the calcium channels regulate and start the process of neurotransmitter release. When Neurontin binds to the alpha-2-delta site in a calcium channel, it does something that we call "modulating" the calcium inflow. Modulating means that Neurontin works similarly to a thermostat, the control on the wall that prevents the temperature from getting too hot or too cold. This was discovered by Fink, Dooley, Feuerstein, and their colleagues in about 1995, and simultaneously by Kathy Sutton and others in Cambridge, England.

This Dooley study is important for understanding how Neurontin works, and I want to explain it to you using the chart from the original published scientific paper that shows the experiment and the results.

Demonstrative 5 (Dooley Study: Neurontin Affects Only Artificially-Stimulated Excess Monoamine Release).

Dr. Dooley's article is titled *Stimulus Dependent Modulation of [^{3}H] Norepinephrine Release from Rat Neocortical Slices by Gabapentin and Pregabalin*. It was published in the Journal of Pharmacology and Experimental Therapeutics in 2000. Dr. Dooley and his team were my colleagues at Parke-Davis and later at Pfizer. Norepinephrine is the neurotransmitter involved in this study. It is one of the "monoamine" neurotransmitters, two others being dopamine and serotonin.

The Dooley study compared the release of norepinephrine from two groups of samples of rat brain tissue. One group of rat brain tissue had been soaked in Neurontin; the other had not been exposed to Neurontin. That allowed them to measure and compare what difference, if any, Neurontin made on neurotransmitter release. The scientists measured how much monoamine was released from the brain tissue samples at five-minute intervals before any stimulus, immediately after a large potassium stimulus forced all of the neurons to dump their monoamines all at once, and at five-minute intervals after the stimulus.

The researchers found that before any external stimulus, Neurontin had no effect at all on monoamine release. But when the tissue samples were shocked by the application of potassium ions, which forced the tissue to release monoamines and other transmitters, both samples did release massive amounts of neurotransmitters, just as they expected. The Neurontin-treated brain tissue, however, showed less of this excessive, forced neurotransmitter release than the untreated sample. In other words, Neurontin "modulated" the excessive release.

This graph shows the actual levels of monoamine release measured in the Dooley study before, at, and after the potassium stimulus. The horizontal line at the bottom of the graph indicates the five-minute intervals where they measured the release. The vertical line on the left measures the amount of monoamine release. Zero would be no release; higher numbers represent higher levels of monoamine release.

The results for both groups, those with and without Neurontin, are plotted on the graph. The black squares show the release in the untreated samples, with no Neurontin. The black triangles show the release in the Neurontin-treated tissue. The lines connect the measurements to make it easier to see any trends in monoamine release over the two hours.

From minute 45 to minute 65 in the study, before any stimulus was applied to force neurotransmitter release, the lines overlap, showing us that Neurontin made no difference at all in neurotransmitter release before the stimulus. At minute 70, the tissue was shocked with potassium to force a massive release of neurotransmitter. We see the release jump up in both samples on the chart.

But for the Neurontin-treated tissue, there is less of the excessive, stimulated release. That is why the Neurontin line—represented by the black triangles—is lower. Thirty minutes later, at the 100 minute mark, you see that both samples, with and without Neurontin, have returned to the level of release at which they started. That is very important, because it shows us that Neurontin did not reduce transmitter release below the normal starting level.

If Neurontin lowered transmitter release below normal levels, you would expect the Neurontin graph—again, the triangles—to be lower than the untreated control sample at every point on the graph, not just in the hyperexcited, potassium stimulated condition. Instead, what

the graph shows is that without the artificial stimulus there is no difference in the monoamine release with or without Neurontin.

This same experiment was repeated in human brain tissue taken from patients who had to have some tissue removed as a part of brain surgery. Also, the study was repeated for the monoamine, noradrenaline, as well as for serotonin, and another neurotransmitter, glutamate. The results in all those studies were similar to those in the Dooley study. Neurontin did not affect transmitter release at all, other than in a hyperexcited state, and in that case, it modulated, or reduced the amount of excessive transmitter release.

This makes sense in terms of what we know about how Neurontin works as a medication. Take Neurontin's two FDA-approved uses—as an adjunctive medication to treat partial complex seizures, and to relieve the form of nerve pain that can follow shingles, called post-herpetic neuralgia. Those are two different diseases, but they both involve excessive signaling in the nervous system that disrupts its normal operation—in one case producing seizures, and in the other, relentless pain. In terms of neuroscience, it makes sense that modulating excessive neurotransmitter release—what the Dooley study demonstrated Neurontin does—would help relieve those two types of conditions.

In my opinion, based on my experience, that is how Neurontin works in the body. It binds to the alpha-2-delta site on the calcium channels, and modulates excessive neurotransmitter release that can occur in situations where the nerves are in an overly excited state, the kind of malfunction of the nervous system that we experience as seizures or pain from damaged nerves. What we have learned about the mechanism of Neurontin in the laboratory makes good sense with what we know about the drug in clinical use.

In his expert report and testimony, Dr. Trimble referred to the drug reserpine and claimed that Neurontin is similar to it. That drug, reserpine, is known to block the release of and to drastically deplete monoamine transmitters like serotonin. In fact, reserpine causes a nearly complete loss of serotonin and other monoamine transmitters in the brain. In contrast, Neurontin has been shown to have no effect on monoamine stores and no effect on monoamine average function in intact humans or animals. There is no scientific study that shows, or even suggests, that Neurontin acts like reserpine in the human body.

Now let's remember that "GABA" is another type of natural neurotransmitter in the brain. Dr. Trimble said in his report and deposition testimony that Neurontin is "GABAergic." I disagree with him. First, the term "GABAergic" has no single definition. If "GABAergic" is taken to mean "affecting the function or working of the GABA system by a specific action at GABA synapses"—which is the definition I would use if asked—then there is absolutely no evidence that Neurontin is GABAergic.

It is important to understand that the generic name for Neurontin, "gabapentin," does not mean that the medication has any effect on the GABA signaling process at synapses in the brain. The molecule that we call Neurontin or gabapentin was given the name "gabapentin" by the U.S. Adopted Names Council ("USANC"), a professional group that assigns names to new compounds based mostly on looking at their chemical formula. Neurontin's generic name relates to what the compound's molecular structure looks like, not what it does. In most cases, the names are issued before the compounds are thoroughly tested and before we know how they work. Gabapentin has its name because the molecule resembles the GABA molecule, not because it is GABAergic. Unfortunately, this has confused many physicians, and others.

Demonstratives 6 and 7 (stick and ball models of GABA and Neurontin)

This is a model of a GABA molecule; this is a model of a Neurontin molecule. The black balls represent carbon atoms, the red balls represent oxygen atoms, the blue balls represent nitrogen atoms, and the white balls represent hydrogen atoms. When the naming agency, USANC, looked at Neurontin, it considered it to be similar to GABA because some of the atoms are the same. As you can see, however, Neurontin has a number of extra parts that the transmitter GABA does not have. They are not the same thing.

Demonstratives 8 and 9 (stick and ball models of L-isoleucine and ammonia)

Even small differences in the structure of two molecules, such as the difference between GABA and Neurontin, can make a big difference in the way they act in the body. For instance, this is a model of the amino acid, L-isoleucine. It is one of the building blocks of protein found in the human body, and it is also in the food we eat. Compare the model of leucine with this molecular model of ammonia. Ammonia is, of course, used as a cleaning product, and is toxic. But the very same molecule that is ammonia is actually a part of isoleucine. Isoleucine makes up a part of the protein in our food; ammonia is poison. Even when molecules have some parts in common, small changes can make big differences in how they act within the body. The fact that there are similarities in the name "GABA" and gabapentin means nothing about how Neurontin works. The fact that there are some similarities in the structure of the neurotransmitter GABA and Neurontin does not mean that they work the same way, at all, in the body.

Demonstrative 10 (FDA Labeling: No GABAergic Activity and No GABA Molecular Target for Neurontin)

The FDA-approved labeling for Neurontin, shown here, confirms that Neurontin does not act on the GABA system as Plaintiff claims. As you can see, FDA clearly states that Neurontin

"does not modify $GABA_A$ or $GABA_B$ radioligand binding." That means that Neurontin does not stick to the same receptors as GABA.

The FDA also says that Neurontin "is not converted metabolically into GABA or a GABA agonist." In other words, Neurontin does not turn into anything that acts like GABA in the human body. Finally, the FDA label says that Neurontin is "not an inhibitor of GABA uptake or degradation," meaning that it does not slow down the normal process of reabsorption or breakdown of GABA. That is, it does not make existing GABA last longer than it otherwise would. All of these statements by FDA are saying that Neurontin does not act like a true "GABAergic" medicine.

If a drug did act in one of these ways—GABA mimicking, GABA agonist, binding at GABA receptors, or slowing the uptake or degradation of GABA—it could be fairly called "GABAergic." But the fact is that, as the FDA labeling says, Neurontin does not work in any of those ways, and that means it is not GABAergic.

Dr. Trimble also cited a couple of papers published by researchers named Petroff and Kuzniecky as support for his claim that Neurontin is "GABAergic." That is not an accurate interpretation of those studies. Petroff and Kuzniecky did not measure the activity of the GABA in the brain after patients took Neurontin. Instead, they only measured the amount of GABA available. Measuring the total amount of GABA in the brain at an instant in time, as Petroff and Kuzniecky did, tells us nothing about whether the drug affects the activity or function of the GABA synapses. It would be like looking in the gas tank of a car to see if something makes a car's engine go faster or slower.

Looking in the gas tank can only tell us how much fuel is available, it does not tell how fast the engine may be running. The Petroff and Kuzniecky studies, similarly, only tell us how

much GABA is present; they tell us nothing about whether there is any increase in GABA function, or if there is an increase, whether it has any real effect on GABA synapses at all.

There is no reliable scientific evidence showing that an increase in whole-brain GABA levels, as opposed to any change in the function of the GABA system, is able to give useful predictions about how the brain is working, much less that it leads to a decrease in serotonin release, and in turn to depression, and then to suicide.

Demonstrative 11 (GABA Levels and Therapies Bar Chart)

In fact, there is a great deal of science that points in the opposite direction. For example, scientists have measured increased GABA levels in the brain after patients were treated with a variety of medicines and therapies that are proven to relieve or reduce depression and suicidality. This includes SSRI antidepressants, electroconvulsive therapy, or ECT, and even simple physical activities like yoga exercise. As this bar graph depicts, elevated GABA levels in the brain have been measured after all of them. It is scientifically absurd to look at the fact that whole-brain GABA levels increase and conclude that a substance or treatment must therefore reduce serotonin, produce depression, and cause suicide. I have never heard or seen any scientist anywhere in the world even suggest this scenario until I heard it in this litigation.

Dr. Trimble claimed in his report that Neurontin is "GABAergic" because it is, he said, a $GABA_B$ agonist. That would mean that it affects a certain GABA receptor, called $GABA_B$. He cited research by a group that included Gordon Ng and Sandrine Bertrand. The findings of Ng and Bertrand have never been replicated outside of their own lab. In contrast, Pfizer and multiple other groups of researchers, repeating the same experiments, have found that Neurontin is not a $GABA_B$ agonist, and those negative results have been published in peer-reviewed journals.

Demonstrative 12 (Neurontin Is Not a GABA Agonist – Jensen (2001) and Lanneau (2002)).

This chart shows two of several studies that found Neurontin is not a $GABA_B$ agonist, which is the opposite of Dr. Trimble's claim about Neurontin in this case. Both the Jensen and Lanneau studies specifically found that Neurontin was not a $GABA_B$ agonist at all.

My own research team at Pfizer also tried to replicate the Ng and Bertrand findings that Dr. Trimble cites. In fact, we would have liked nothing more than to have been able to replicate their findings, because if we had found that Neurontin was a $GABA_B$ receptor agonist, that not only would have increased our understanding of how the drug works, it potentially could have led to new medical uses for Neurontin. We did exactly what Ng and Bertrand said they did, but, like Jensen's and Lanneau's teams, we found no action by Neurontin on $GABA_B$ receptors. In my opinion, the fact that three different research groups were unable to replicate the results of Ng and Bertrand indicates that those results are not scientifically reliable, and therefore are a poor source to base a theory upon.

Demonstrative 13 (Plaintiff's Expert's Theory)

Dr. Trimble claimed in his report and deposition in this case that Neurontin elevates GABA levels in the brain, and that the elevation can lead to a cascade of events culminating in suicide. This chart just lays out the steps in Dr. Trimble's theory that I heard him testify to in his deposition.

Although I have been researching Neurontin for more than 25 years, the first time I ever heard of this five-step hypothesis was in this case. Neurontin was first discovered in a Parke-Davis laboratory in Germany in 1975. It was first given to and tested in humans in 1982. By the mid-1980s, several human clinical drug trials were underway. In the thirty-five years since Neurontin was discovered, a huge number of peer-reviewed studies on the drug have been

published in medical and scientific journals. In the PubMed database, which is a comprehensive collection of scientific literature maintained by the federal government's National Institutes of Health ("NIH"), there are more than 1,300 studies with Neurontin (or gabapentin) in the title.

As a scientist involved in researching Neurontin, it was part of my job to be familiar with that literature. I have never seen a single published article in which any scientist suggested that taking Neurontin would elevate GABA, lower serotonin, cause depression, and then cause suicide or suicide-related thoughts. The FDA's analysis of suicidality and antiepileptic medicines does not endorse Plaintiff's theory. In fact, not one part of the Plaintiff's theory is mentioned in any of the FDA's analysis or in any of the FDA Advisory Committee's discussion on the subject. That theory, as far as I can tell, exists only in this litigation.

C. Neurontin and Depression and Suicide

Let me now address the steps in Dr. Trimble's theory that taking Neurontin increases GABA, which eventually leads to depression and then suicide.

Demonstrative 14 (Schatzberg & Nemeroff (3d ed. 2004))

The relationship between GABA and depression is discussed in the scientific literature, and in psychopharmacology textbooks. One example is Schatzberg's and Nemeroff's *Textbook of Psychopharmacology* (3d ed. 2004), shown here. This book is recognized as authoritative in the field of psychopharmacology, which is the study of medicines used to treat psychiatric patients and those with other conditions that affect the brain.

Schatzberg and Nemeroff summarize the scientific knowledge of the relationship between GABA levels and depression on page 736 of the textbook. The authors explain that low levels of GABA in the brain are associated with both depression and the severity of depression. In other words, people with depression are more likely to have low GABA levels than high GABA levels. And people who have severe depression on average have lower GABA levels

than people who are not as severely depressed. The scientific studies cited in Schatzberg and Nemeroff say the same thing: low GABA is associated with depression.

That is exactly the opposite of the theory that Dr. Trimble has stated in this case—he says higher brain GABA levels lead to depression. The science says just the opposite, that lower GABA levels in the brain are associated with depression. As we saw earlier, many antidepressant medicines and treatments like ECT that are proven to reduce depression are associated with increased brain GABA levels. Even yoga is associated with higher GABA levels—the same change in GABA levels that Dr. Trimble says leads to suicide. In my opinion, that second step of his theory is completely inconsistent with the science about the relationship between GABA and depression.

Now let me address the third step in Dr. Trimble's theory, that after Neurontin elevates GABA levels, it decreases serotonin release and produces depression. Earlier we looked at Dr. Dooley's study, the one that measured Neurontin's effect on the release of one of the monoamine transmitters, norepinephrine, in brain tissue samples, and that first found the "modulating" effect that I told you about. As I mentioned, that finding also was confirmed in human brain tissue and with other neurotransmitters, including serotonin.

I explained how hard it is to directly study human brain tissue, and it is. But it is possible to look for evidence of changes in monoamines like serotonin in the cerebrospinal fluid that surrounds the brain and spinal cord in living patients' central nervous systems. Even studying cerebrospinal fluid is difficult, because to do it, you need volunteer subjects who are willing to undergo a spinal tap procedure, the only way we can draw cerebrospinal fluid from living people. It is quite uncomfortable and so it is not often done.

But in 1995, there was a study of just that kind. It gives us very important information about the actual effect of Neurontin on serotonin, norepinephrine, and dopamine, the neurotransmitters that regulate mood, as well as the neurotransmitter GABA, in living humans.

Demonstrative 15 (Ben-Menachem (1995): Neurontin Does Not Affect GABA or Serotonin Turnover)

In 1995, a research team headed by Dr. Elinor Ben-Menachem in Sweden studied Neurontin's effect on the levels of transmitters in the brain by analyzing human cerebrospinal fluid.

Dr. Ben-Menachem and her team first took cerebrospinal fluid samples and measured the levels of GABA and the breakdown products of serotonin and noradrenaline before the patients had taken any Neurontin. That told them what the patients levels were at the start, so that they could compare measurements after the patients took Neurontin to examine any possible drug effects. The researchers then took new samples of cerebrospinal fluid and made the same measurements after the patients used either 900 or 1200 mg of Neurontin for three months. The same measurements were made in a second, separate group that was given an inactive placebo pill. That is important because it provided a way to make sure that any differences seen are due to the medication, and not merely the passage of time or some other factor that affected all the patients.

Dr. Ben-Menachem's measurements indicated that "there were no changes in the selected amino acids, HVA, or 5-HIAA after treatment." This is a direct quote from the paper by Dr. Ben Menachem. Let me explain what those letters and numbers mean.

5-HIAA refers to the natural breakdown product of serotonin; it correlates to serotonin turnover, or the rate at which the system is making, releasing, and breaking down serotonin. HVA is the natural breakdown product of dopamine and norepinephrine, and correlates to the

rate of releasing those transmitters. The bottom line is that none of the levels changed with Neurontin, indicating that Neurontin did not alter serotonin function like some other drugs do.

Dr. Ben-Menachem's published findings go directly against Dr. Trimble's theory. If Neurontin raised GABA and then lowered serotonin the way he claims, Dr. Ben-Menachem would have seen significantly lower levels of 5-HIAA after three months in the patients treated with Neurontin. Instead, the results were no change in serotonin or norepinephrine turnover.

Dr. Ben-Menachem's study is the only one that directly measured these chemicals in the brain fluid of live human subjects before and after Neurontin treatment. Anyone interested in reviewing the available medical literature on Neurontin and its effects on GABA and monoamine levels could easily find it; a simple search of the PubMed database for articles with the words "Neurontin, gabapentin, CSF, and GABA" will locate it in just a few seconds. Yet Dr. Trimble did not even mention this crucial study anywhere in his report.

To my knowledge, there is no reliable scientific evidence that supports the theory that Neurontin reduces levels, turnover, or function of serotonin or any other monoamine, to any clinically significant degree, in living human patients. In contrast, Dr. Ben-Menachem studied the effect of Neurontin in cerebrospinal fluid from living people, and found no change. A similar study done in animals found the same results—no effect on monoamine turnover with Neurontin. To put it very simply, there is no reliable scientific evidence that Neurontin depletes monoamines; there is reliable scientific evidence that it does not have that effect at all.

III. SUMMARY OF OPINIONS

I have reached my opinions in this case, which I hold to a reasonable degree of scientific certainty, based on my education, training, professional expertise, and experience as a research scientist. In addition, my opinions are based on all of my 25 years of research specifically regarding Neurontin. My opinions are summarized in this chart.

Demonstrative 16 (Summary of Opinions)

Dr. Trimble is incorrect that Neurontin acts in the brain in any way that is expected to produce depression or suicide.

Neurontin binds to the calcium channel alpha-2-delta site. That drug binding modulates or calms overactive neurons. This calming action makes Neurontin useful to reduce seizures, reduce pain, and reduce anxiety.

Neurontin does not increase GABA activity in the brain. Several other drugs do act directly at GABA synapses to increase GABA function, but Neurontin does not do that.

Neurontin also does not change serotonin function in the brain. We saw that in the Ben-Menachem study, the study that measured this in cerebrospinal fluid, a very relevant part of the brain. Dr. Ben-Menachem found no change in GABA or serotonin function with Neurontin treatment.

It is incorrect for Dr. Trimble to say that Neurontin is a GABAergic drug. There are drugs that are correctly labeled as "serotonergic," "GABAergic," "dopaminergic," etc. All of these medicines act at sites unique to one type of synapse. Neurontin does not do this.

Dr. Trimble is also incorrect that elevated whole-brain GABA levels cause depression and suicide. In fact, just the opposite is true. Low brain GABA levels are associated with depression. Antidepressant treatments and yoga exercise each increase brain GABA levels. Even if a treatment increases the total amount of GABA in the brain, there is no reliable scientific evidence showing that this change causes depression or suicide.

I have written a number of scientific papers expressing my opinions of how Neurontin works. My papers have been examined and approved by peer review committees before they were published. In contrast, Dr. Trimble's theory, which, if true, would affect the health and

safety of millions of patients, has never been published or even presented outside of a lawsuit, and has never been subjected to scientific peer review.

The bottom line is that nothing we have discovered about Neurontin suggests that it has any action that increases depression or suicidality. The best available science indicates that Neurontin does not have those effects.

On the other hand, the science shows us that Neurontin does calm the activity of overactive neurons. This explains why Neurontin reduces seizures, nerve pain, and anxiety. Neurontin therapy for seizures, nerve pain, and anxiety has been proven in double-blind, placebo-controlled clinical studies published in peer-reviewed journals. These studies are the gold standard of evidence of clinical drug effects—what a drug actually does in humans, including adverse drug effects. Consistent with everything that I have just told you about how Neurontin works in the brain, none of these clinical study results, or even other unpublished placebo-controlled results, even hint that Neurontin could cause depression or suicidality.